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MINNESOTA UNIV MINNEAPOLIS DEPT OF CHEMISTRY
SYNTHESIS OF ANTIMALARIALS BY A NEW ROUTE TO 4-QUINOLINOLS, 4-Q--ETC(U)
MAR 77 W E NOLAND

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Synthesis of Antimalarials by a New Route to
4-Quinolinols, 4-Quinazolinones, and 4-Cinnolinol 1-Oxides

Final Scientific Report

Contract Period: June 22, 1967-Dec. 31, 1969 (2 1/2 years)

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By

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Summary

Nine target compounds, six 4-(4-diethylamino-1-methylbutylamino)-3-phenylquinolines (1) and three 4-(4-diethylamino-1-methylbutylamino)-3-phenylquinazolines (2), and 100 intermediates were prepared and submitted for testing. All six of the quinoline antimalarials (1) showed some evidence of activity, and four of them, containing 4-methoxy (1a), 4-unsubstituted (1c), 4-bromo (1d), and 4-nitro (1e) substituents in the 3-phenyl group were classed as active in mice, though only the methoxy derivative (1a) was classed as active at a dosage (320 mg/kg) below that at which some toxic deaths were observed. Three of the compounds, 1a, 1c, and 1e, were classed as active in chicks at dosages (80, 320, and 320 mg/kg, respectively) where no toxic deaths were observed. Although all three were submitted, only one of the quinazoline antimalarials, the 6-chloro-2-phenyl derivative (2c), was tested in mice; it showed strong evidence of activity, but not quite sufficient to be classed as active.

None of the 100 intermediates were classed as active in mice, but the best evidence of activity was observed with the following compounds (in decreasing order):

4-chloroanthranilic acid hydrochloride (16c) 80 mg/kg
T-C 3.1 days

N-(3,4-dichlorobenzoyl)isatin (18c) 160 T-C 3.1 and 2.9

Compound 11a 640 T-C 3.9

2-(4-nitrophenyl)isatogen (3e) 640 T-C 3.5

sodium 6-chloro-2-(3,4-dichlorophenyl)quinazoline-4-carboxylate
(12h) 640 T-C 2.9

methyl 6-chloro-2-(3,4-dichlorophenyl)quinazoline-4-carboxylate
(12i) 640 T-C 2.5

(continued)

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Summary - continued

6-chloroanthranilic acid (16g) 640 T-C 2.3

4,6-dichloro-3-(4-methoxyphenyl)quinoline (8f) 640 T-C 1.8

4-chloro-3-(4-methylphenyl)quinoline (8b) 640 T-C 1.4

1-cinnamylpyridinium chloride (19) 160 T-C 1.3

6-chloro-2-nitrobenzoic acid (22) 640 T-C 1.3

methyl 5-chloro-N-(4-nitrobenzoyl)anthranilate (17i) 640 T-C 1.1

More complete details are provided in the List of Compounds Prepared and Submitted for Testing which follows.

Financial support for the contract was discontinued by its sponsor after it was decided that the 4-aminoquinoline (1) and 4-aminoquinazoline (2) antimalarials would have to compare favorably with chloroquine, and the 2-phenyl-4-quinazoline aminoalcohols (the synthesis of which was not completed) would have to be free of or very low in phototoxicity, which was considered unlikely.

Note added: While approval of this report was being awaited, samples of a number of the new compounds for which elemental analyses had not been reported (and which are now over eight years old) were subjected to mass spectral analysis, without further purification. The mass spectral results are reported as footnotes to the tables where descriptions of the compounds appear. In some cases the results support the formulas and structures assigned. In other cases they show that, at least in their present state, the samples are not what had been thought or are mixtures. This underlines the fact that, in the absence of supporting elemental analyses and/or mass spectral verification of molecular weight, the structures assigned to those new compounds which are included in the tables should be viewed with a healthy degree of skepticism.

Antimalarial Test Results

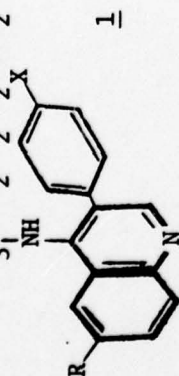
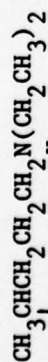
For the tests designated with (infected) mice or chicks the date (day/month/year) of the computer printout is then given in parentheses, followed by the highest dosage given (subcutaneously), in mg./kg. of body weight, which did not cause toxic deaths. This is followed by the change in mean survival time in days, T-C (mean survival time of treated animals - mean survival time of controls), and then the corresponding data for higher dosages, if any, which caused toxic deaths as noted. Compounds are designated as active when an increase of 100% or more in mean survival time is observed.

With mosquito screening tests, designated as P. gall. A. aegypti, Plasmodium gallinaceum (Strain B) was used to infect a standard strain of Aedes aegypti. The date (day/month/year) of the computer printout is then given, followed by the concentration of the test compound, 0.1% unless toxic deaths were found to be predominant, in the 10% sucrose solution fed to the mosquitos. This is followed by the % of toxic deaths observed relative to a control and then by any observations of abnormal oocysts or suppression of oocysts or sporozoites, or their absence, designated by neg.

- 1a mice (31/07/68) 320 T-C 6.1 active, 640 T-C 7.9 active but 3 toxic deaths at 4 days, 640 T-C 8.9 active but 2 toxic deaths at 4 days; chick (01/10/68, 19/11/68) 80 T-C 3.7 active, 160 T-C 5.0 active but 1 toxic death at 1 day; P. gall. A. aegypti (26/06/69) 0.1% 6% toxic deaths (control 9%) neg.
- 1b mice (14/04/69) 640 T-C 1.8 but 3 toxic deaths at 4 days; P. gall. A. aegypti (17/04/69) 0.01% 9% toxic deaths (control 9%) neg., 0.1% 100% toxic deaths (control 26%)
- 1c mice (31/07/68) 160 T-C 5.3 (01/10/68) 160 T-C 4.9, 320 T-C 8.2 active but 1 toxic death at 4 days, 640 T-C 9.7 active but 3 toxic deaths at 4 days; chick (31/07/68) 320 T-C 6.7 active (16/01/69) 480 T-C 5.5 active; P. gall. A. aegypti (26/09/69) 0.1% 63% toxic deaths (control 23%) neg.
- 1d mice (31/07/68) 320 T-C 5.1, 640 T-C 8.4 active but 3 toxic deaths at 4 days, 640 T-C 8.9 active but 3 toxic deaths at 4 days; P. gall. A. aegypti (26/06/69) 0.1% 74% toxic deaths (control 9%) neg.
- 1e mice (21/08/68) 160 T-C 4.3, 320 T-C 6.9 active but 1 toxic death at 4 days (01/10/68) 160 4.3, 320 T-C 8.9 active but 1 toxic death at 4 days; chick (31/07/68) 320 T-C 6.5 active; P. gall. A. aegypti (26/06/69) 0.1% 11% toxic deaths (control 9%) neg.
- 1f mice (14/04/69) 640 T-C 0.8; P. gall. A. aegypti (17/04/69) 0.01% 26% toxic deaths (control 9%) neg., 0.1% 100% toxic deaths (control 26%)

I. Target Compounds

A. 4-(4-Diethylamino-1-methylbutylamino)-3-phenylquinolines



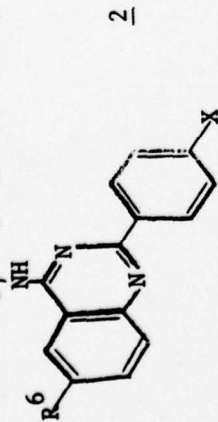
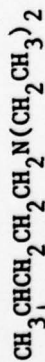
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1	X	R	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source and Reference
a	OCH ₃	H	3-(4-methoxyphenyl)	67-70	C ₂₅ H ₃₃ N ₃ O 391.54	C 76.68 H 8.50 N 10.73 76.64 8.61 10.74		MAS
b	CH ₃	H	3-(4-methylphenyl)	62-63	C ₂₅ H ₃₃ N ₃ 375.54	C 79.95 H 8.86 N 11.19 79.84 8.81 11.13		MAS
c	H	H	3-phenyl	59-61	C ₂₄ H ₃₁ N ₃ 361.51	C 79.73 H 8.64 N 11.62 79.67 8.47 11.44		MAS
d	Br	H	3-(4-bromophenyl)	70	C ₂₄ H ₃₀ N ₃ Br 440.42	C 65.45 H 6.87 N 9.54 Br 18.15 65.69 7.19 9.63 16.20		MAS
e	NO ₂	H	3-(4-nitrophenyl)	brown oil	C ₂₄ H ₃₀ N ₃ O ₂ 406.51	C 70.91 H 7.44 N 13.78 70.82 7.68 13.61		MAS
f	OCH ₃	Cl	6-chloro-3-(4-methoxyphenyl)	oil	C ₂₅ H ₃₂ N ₃ OC1 425.99	C 70.48 H 7.57 N 9.87 Cl 8.32 70.40 7.59 9.86 7.59		MAS

1	Our No.	Walter Reed No.	Sample Size, g.	Date Received
a	NS-29	AD 22742	2.5	01/05/68
b	NS-48	AF 52562	2.5	29/10/68
c	NS-6	AD 22706	2.5	01/05/68
d	NS-32	AD 22751	2.5	01/05/68
e	NS-28	AD 22733	2.5	01/05/68
f	NS-53	AF 52606	2.5	29/10/68

I. Target Compounds - continued

B. 4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinazolines



<u>2</u>	<u>X</u>	<u>R⁶</u>	<u>Substituent Identification</u>	<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source and Reference</u>
<u>a</u>	OCH ₃	H	2-(4-methoxyphenyl)	oil	C ₂₄ H ₃₂ N ₄ O 392.53	C 73.43 H 8.22 72.35 8.33	N 14.27 14.00	MAS
<u>b</u>	H	H	2-phenyl	oil	C ₂₃ H ₃₀ N ₄ 362.50	C 76.20 H 8.34 76.36 8.47	N 15.46 15.19	MAS ^a
<u>c</u>	H	Cl	6-chloro-2-phenyl	78-86	C ₂₃ H ₂₉ N ₄ Cl 396.95	C 69.59 H 7.36 69.71 7.70	N 14.12 Cl 14.08 8.78	KTK
<u>c'</u>	H	Cl	6-chloro-2-phenyl, sesquihydrochloride (= ·1.5 HCl)	yellow solid	C ₂₃ H ₂₉ N ₄ Cl · 1.5 HCl 451.65	C 61.16 H 6.81 61.32 6.81	N 12.41 Cl 12.02 21.03	KTK

<u>2</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	NS-85	AU 24947	2.5	28/05/69
<u>b</u>	NS-80	AU 24929	2.0	28/05/69
<u>c</u>	JM-45-E	WR 93216-A?	1.85	14/12/67
<u>c'</u>	JM-20-G	WR 93216-B?	1.0	14/12/67

2a P. gall. A. aegypti (05/11/69) 0.1% 90% toxic deaths (control 3%) neg.

2b P. gall. A. aegypti (05/11/69) 0.1% 40% toxic deaths (control 0%) 25% oocyst suppression (control 0%) otherwise neg.

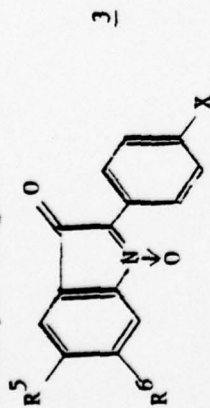
2c mice (04/04/68, Group 613) 640 T-C 4.0 (04/04/68, Group 615) 640 T-C 3.1; P. gall. A. aegypti (15/05/68) 0.01% 0% toxic deaths neg., 0.1% 100% toxic deaths

2c' no report (unless included under 2c)

II. Intermediates

A. Isatogens

1. 2-Phenylisatogens



<u>3</u>	<u>X</u>	<u>R⁵</u>	<u>R⁶</u>	Substituent Identification	mp°	Formula Mol. Wt.	Anal.		Calcd. % Found	Source and Reference
<u>a</u>	CH ₃ O	H	H	2-(4-methoxyphenyl)	187-188 193 ^b violet needles	C ₁₅ H ₁₁ NO ₃ 253.25	C 71.14 ^b 70.93 ^b	H 4.37 ^b 4.46	N 5.53 ^b 5.81 ^b	TRA ^{b,c}
<u>b</u>	CH ₃	H	H	2-(4-methylphenyl)	208-209 red needles	C ₁₅ H ₁₁ NO ₂ 237.25	C 75.93 75.85	H 4.67 4.56	N 5.90 5.94	MAS
<u>c</u>	H	H	H	2-phenyl	188-189 189.5-190.5 ^d 189-190 ^d orange needles	C ₁₄ H ₉ NO ₂ 223.22	C 75.32 ^d 75.46 ^d 75.52 ^d	H 4.06 ^d 4.25 ^d 4.34 ^d	N 6.28 ^d 6.25 ^d 6.32 ^d	MAS ^{d,e}
<u>d</u>	Br	H	H	2-(4-bromophenyl)	186-187 orange-red	C ₁₄ H ₈ NO ₂ Br 302.13	C 55.65 55.37	H 2.67 2.78	N 4.64 4.57	MAS
<u>e</u>	NO ₂	H	H	2-(4-nitrophenyl)	261-262 250-254 dec ^{ea} orange-red	C ₁₄ H ₈ N ₂ O ₄ 268.22	C 62.69 ^{ea} 62.61 ^{ea} 62.90 ^{ea}	H 3.01 ^{ea} 3.08 ^{ea} 3.01 ^{ea}	N 10.45 ^{ea} 10.50 ^{ea} 10.59 ^{ea} 10.48	MAS ^{e,fa}
<u>f</u>	CH ₃ O	Cl	H	5-chloro-2-(4-methoxyphenyl)	235-236 brown needles	C ₁₅ H ₁₀ NO ₃ Cl 287.70	C 62.62 62.38	H 3.50 3.41	N 4.87 4.83	MAS
<u>g</u>	CH ₃	Cl	H	5-chloro-2-(4-methylphenyl)	180-180.5 orange plates	C ₁₅ H ₁₀ NO ₂ Cl 271.70	C 66.31 66.03	H 3.71 3.66	N 5.15 5.07	MAS
<u>h</u>	H	Cl	H	5-chloro-2-phenyl	182-183 orange-red	C ₁₄ H ₈ NO ₂ Cl 257.67	C 65.25 65.07	H 3.13 3.22	N 5.44 5.45	MAS

II. Intermediates

A. Isatogens

1. 2-Phenylisatogens - continued

<u>3</u>	<u>X</u>	<u>R</u> ⁵	<u>R</u> ⁶	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source and Reference
<u>i</u>	H	NO ₂	H	5-nitro-2-phenyl	240-241 234-235 240-243 ^{ga} 238-239 ^{gb} orange plates 210-211 ^{ha} 206 ^{ha} red plates	C ₁₄ H ₈ N ₂ O ₄ 268.22	C 62.69 61.39 62.63 ^{ga} 62.81 ^{gb} H 3.01 2.88 3.16 ^{ga} 3.31 ^{gb}	N 10.45 10.33 10.59 ^{ga} 10.31 ^{gb}	MAS ^{fa,8}
<u>j</u>	H	H	NO ₂	6-nitro-2-phenyl		C ₁₄ H ₈ N ₂ O ₄ 268.22	C 62.69 ^{ha} 63.39 ^{ha} 62.70 ^{ha} H 3.01 ^{ha} 3.35 ^{ha} 3.46 ^{ha}	N 10.45 ^{ha} 10.34 ^{ha}	JOB ^{fa,h}

<u>3</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	TRA-84-1	AC 66178	0.5	04/03/68
<u>b</u>	NS-45	AF 52535 AU 66267	0.5 0.3	29/10/68 23/06/69
<u>c</u>	MAS-3	AC 66123	0.5	04/03/68
<u>d</u>	MAS-19	AC 66150	0.5	04/03/68
<u>e</u>	MAS-9	AC 66132	0.5	04/03/68
<u>f</u>	NS-50	AF 52571	0.5	29/10/68
<u>g</u>	NS-89	AV 58091	0.3	01/12/69
<u>h</u>	MAS-15	AC 66141	0.5	04/03/68
<u>i</u>	MAS-26	AC 66169	0.5	04/03/68
<u>j</u>	JB8J	AC 66114	0.5	04/03/68

II. Intermediates

A. Isatogens

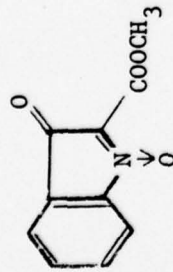
1. 2-Phenylisatogens - continued

- 3a mice (06/12/68) 640 T-C 0.5; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 23% toxic deaths (control 17%) neg.
- 3b mice (14/04/69) 640 T-C 0.8
- 3c mice (06/12/68) 640 T-C 0.5; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 17% toxic deaths (control 17%) neg.
- 3d mice (06/12/68) 640 T-C 0.9 but 3 toxic deaths at 4 days; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 9% toxic deaths (control 17%) neg.
- 3e mice (01/07/68) 640 T-C 3.5 (06/12/68) 640 T-C 3.9; P. gall. A. aegypti (10/10/68) 0.1% 26% toxic deaths (control 17%) neg.
- 3f mice (14/04/69) 640 T-C 1.2
- 3g no report
- 3h mice (06/12/68) 640 T-C 0.7; chick (02/10/71) 320 T-C 0 but 1 toxic death at 1 day; P. gall. A. aegypti (10/10/68) 0.1% 14% toxic deaths (control 17%) neg.
- 3i mice (06/12/68) 640 T-C 0.3; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 26% toxic deaths (control 17%) neg.
- 3j mice (31/07/68) 640 T-C 0.3; P. gall. A. aegypti (10/10/68) 0.1% 9% toxic deaths (control 3%) 75% oocyst suppression (control 25%) otherwise neg.

II. Intermediates

A. Isatogens - continued

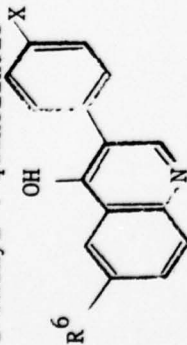
2. Methyl Isatogen-2-carboxylate



<u>4</u>	<u>mp°</u>	<u>Formula</u> <u>Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. %</u>		<u>Source</u> <u>and</u> <u>Reference</u>	<u>Our No.</u>	<u>Walter</u> <u>Reed No.</u>	<u>Sample</u> <u>Size, g.</u>	<u>Date</u> <u>Received</u>
				<u>Found</u>	<u>N</u>					
a	201-202 201 ^{hb}	C ₁₀ H ₇ NO ₄ 205.16	C 58.54 H 3.44 N 6.83 ^{hb} 7.09 ^{hb}			SYA ^{hb}	A-1	AD 22671	0.5	01/05/68

4 mice (31/07/68) 640 T-C 0.9 but 2 toxic deaths at 4 days; P. gall. A. aegypti (26/06/69) 0.1% 6% toxic deaths (23% control) neg.

B. 3-Phenyl-4-quinolinols



<u>5</u>	<u>X</u>	<u>R⁶</u>	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source and Reference
<u>a</u>	OCH ₃	H	3-(4-methoxyphenyl)	295-297	C ₁₆ H ₁₃ NO ₂ 251.27	C 76.47 76.48 H 5.22 5.16	N 5.57 5.33	MAS
<u>b</u>	CH ₃	H	3-(4-methylphenyl)	284-285	C ₁₆ H ₁₃ NO 253.27	C 81.68 81.38 H 5.57 5.39	N 5.95 5.70	MAS
<u>c</u>	H	H	3-phenyl	258-260 261.5-262 ^{fa}	C ₁₅ H ₁₁ NO 221.25	C 81.43 ^{fa} 81.56 ^{fa} H 5.01 ^{fa} 5.08 ^{fa}	N 6.33 ^{fa} 6.18 ^{fa}	MAS ^{fa,i,j}
<u>d</u>	Br	H	3-(4-bromophenyl)	312-314	C ₁₅ H ₁₀ NOBr 300.15	C 60.02 60.14 H 3.36 3.49	N 4.66 4.49	MAS
<u>e</u>	NO ₂	H	3-(4-nitrophenyl)	363-364 368-369 ^{dec}	C ₁₅ H ₁₀ N ₂ O ₃ 266.25	C 67.66 ^{fb,i} 67.50 ^{fb,i} H 3.79 ^{fb,i} 3.95 ^{fb,i}	N 10.52 ^{fb,i} 10.27 ^{fb,i}	MAS ^{fb,i}
<u>f</u>	OCH ₃	Cl	6-chloro-3-(4-methoxyphenyl)	359-360	C ₁₆ H ₁₂ NO ₂ Cl 285.72	C 67.25 67.37 H 4.24 4.16	N 4.90 4.64	MAS
<u>g</u>	H	NO ₂	6-nitro-3-phenyl	351-352 350-352 (turns black) ^{fb}	C ₁₅ H ₁₀ N ₂ O ₃ 266.25	C 67.66 ^{fb} 67.94 ^{fb} H 3.79 ^{fb} 4.07 ^{fb}	N 10.52 ^{fb} 10.85 ^{fb}	MAS ^{fb,ja}

II. Intermediates - continued

B. 3-Phenyl-4-quinolinols

<u>5</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	NS-26	AD 55965	0.5	17/05/68
	NS-26A	AE 06789	0.25	11/06/68
<u>b</u>	NS-46	AF 52544	0.5	29/10/68
<u>c</u>	NS-4	AD 22680	0.5	01/05/68
<u>d</u>	NS-30	AD 55983	0.5	17/05/68
	NS-4A	AF 11427	0.5	24/09/68
<u>e</u>	NS-10	AD 22715	0.5	01/05/68
<u>f</u>	NS-51	AF 52580	0.5	29/10/68
<u>g</u>	NS-33	AD 22760	0.5	01/05/68

5a P. gall. A. aegypti (06/11/68) 0.1% 11% toxic deaths (control 6%) 100% oocyst suppression (control 0%) otherwise neg.

5b mice (14/04/69) 640 T-C 0.2

5c mice (31/07/68) 160 T-C 0.7; chick (31/07/68) 320 T-C 0.1; P. gall. A. aegypti (10/10/68) 0.1% 17% toxic deaths (control 3%) 25% oocyst suppression (control 0%) 50% sporozoite suppression (control 0%), 0.1% no toxic deaths (control 6%) neg. (thus, not confirming the previous run)

5d mice (21/08/68) 640 T-C 0.7

5e mice (31/07/68) 640 T-C 0.1

5f mice (14/04/69) 640 T-C 0.2

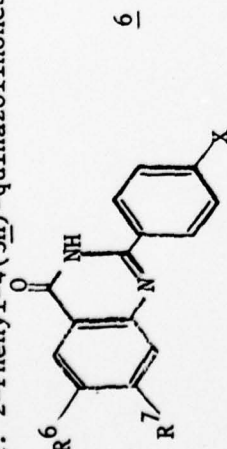
5g mice (31/07/68) 640 T-C 0.8; P. gall. A. aegypti (26/06/69) 0.1% 17% toxic deaths (control 9%) 25% oocyst suppression (control 0%)

II. Intermediates - continued

13

C. 4(3H)-Quinazolinones

1. 2-Phenyl-4(3H)-quinazolinones



<u>6</u>	<u>X</u>	<u>R⁶</u>	<u>R⁷</u>	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source and Reference
<u>a</u>	OCH ₃	H	H	2-(4-methoxyphenyl)	246-248, kb 257-259 250-251 240-241	C ₁₅ H ₁₂ N ₂ O ₂ 252.26	C 71.41, kb 71.65 71.18 75.65 75.75	N 11.11, kb 11.29 10.89 12.61 12.61	JBH ¹ MAS ¹ MAS ^{a, lb, lc, ld}
<u>b</u>	H	H	H	2-phenyl		C ₁₄ H ₁₀ N ₂ O 222.24	H 4.54 4.46	N 12.61 12.61	
<u>c</u>	NO ₂	H	H	2-(4-nitrophenyl)	363-365	C ₁₄ H ₉ N ₃ O ₃ 267.24	H 3.39, kb 3.52	N 15.73, kb 15.99	JBH ^{1a, lc, m}
<u>d</u>	H	Cl	H	6-chloro-2-phenyl	298-300 298 dec 295-297	C ₁₄ H ₉ N ₂ OCl 256.68	C 65.51, ka 63.50	N 10.92, ka 10.51	JBH ^{ld, n} KTK ^{ld, n}
<u>e</u>	NO ₂	Cl	H	6-chloro-2-(4-nitrophenyl)	317-320 dec 285-300	C ₁₄ H ₈ N ₃ O ₃ 301.68	C 55.74 -	N 13.93 -	JBH ^{kb} KTK
<u>f</u>	H	H	Cl	7-chloro-2-phenyl	271-281 292 ⁿ	C ₁₄ H ₉ N ₂ OCl 256.68	C 65.51 -	N 10.92 10.60 ⁿ	KTK ⁿ

13

II. Intermediates

14

C. 4(3H)-Quinazolinones

1. 2-Phenyl-4(3H)-quinazolinones - continued

<u>6</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JH I-13-14 gift NS-78	WR-93221-A AU 24901	0.45 0.5	14/12/67 28/05/69
<u>b</u>	NS-66	AU 24894	0.5	28/05/69
<u>c</u>	JH I-17-16 gift	WR-93220-A	0.62	14/12/67
<u>d</u>	JH I-41-30 gift JM-4 (JH-JH)	WR-93219-A AW 98545	0.5 0.6	14/12/67 16/04/70
<u>e</u>	JH I-57-2 gift JM-55	WR-93218-A AW 49462	0.5 0.4	14/12/67 16/04/70
<u>f</u>	JM-114	AW 49480	0.6	16/04/70

6a mice (04/04/68) 640 T-C 0 (05/11/69) 160 T-C 0.2; P. gall. A. aegypti (15/05/68) 0.1% 14% toxic deaths neg.

6b mice (05/11/69) 160 T-C 0.6

6c P. gall. A. aegypti (15/05/68) 0.1% 17% toxic deaths neg.

6d mice (04/04/68) 640 T-C 0.2 (23/09/70) 640 T-C 0.7; chick (10/02/71) 160 T-C 0; P. gall. A. aegypti (15/05/68) 0.1% 3% toxic deaths 25% oocyst suppression

6e mice (04/04/68) 640 T-C 0.6 (07/08/70), 23/09/70) 640 T-C 0.1; P. gall. A. aegypti (15/05/68) 0.1% 6% toxic deaths neg.

6f mice (04/04/68) 640 T-C 0 (07/08/70) 640 T-C 0.5

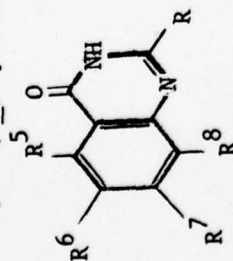
14

II. Intermediates

15

C. 4(3H)-Quinazolinones - continued

2. 2-Alkyl-4(3H)-quinazolinones



7

7	R	R ⁵	R ⁶	R ⁷	R ⁸	Substituent Identification	mp°	Formula Mol. Wt.	Anal.		Calcd. %		Reference
a	CH ₃	H	H	H	H	2-methyl	245.5-246.5	C ₉ H ₈ N ₂ O 160.17	C 67.48	H 5.03	N 17.49	-	KTK
b	CF ₃	H	H	H	H	2-trifluoro- methyl*	218-221	C ₉ H ₅ N ₂ OF ₃ 214.15	C 50.48	H 2.35	N 13.08	-	KTK
c	CCl ₃	H	H	H	H	2-trichloro- methyl	219.5-221	C ₉ H ₅ N ₂ OC1 ₃ 263.52	C 41.02	H 1.91	N 10.63	Cl 40.37	KTK
d		H	H	H	H	2-cyclohexyl	230-231 226-227	C ₁₄ H ₁₆ N ₂ O 228.28	C 73.65	H 7.06	N 12.27	-	KTK ^o
e		H	H	H	H	2-cyclohexyl, hydrochloride	225-227	C ₁₄ H ₁₇ N ₂ OC1 264.75	C 63.51	H 6.47	N 10.58	Cl 13.39	KTK
f	CCl ₃	H	Cl	H	H	6-chloro-2-tri- chloromethyl	262.5-264.5	C ₉ H ₄ N ₂ OC1 ₄ 297.97	C 36.28	H 1.35	N 9.40	Cl 47.60	KTK
g	CCl ₃	H	H	NO ₂ [#]	H	7-nitro-2-tri- chloromethyl [#]	243-246	C ₉ H ₄ N ₃ O ₂ Cl ₃ 308.52	C 35.03	H 1.31	N 13.62	Cl 34.48	KTK
h	CCl ₃	H	H	Cl	H	7-chloro-2-tri- chloromethyl	238-242 239-241	C ₉ H ₄ N ₂ OC1 ₄ 297.97	C 35.48	H 1.35	N 9.40	Cl 47.60	KTK
i		Cl	H	H	H	5-chloro-2- cyclohexyl [†]	188-194	C ₁₄ H ₁₅ N ₂ OC1 [†] 262.73	C 64.00	H 5.75	N 10.66	Cl 13.50	KTK
j		H	Cl	H	H	6-chloro-2- cyclohexyl	285-286.5	C ₁₄ H ₁₅ N ₂ OC1 262.73	C 64.00	H 5.75	N 10.66	Cl 13.50	KTK

(footnotes are on next page)

*Molecular formula and structure are in doubt.

#The position of the nitro group is given incorrectly as 6- in the name and structure on the data sheet for this compound.

†High resolution mass spectrum m/e 262.0916 (M^+ , calcd for $C_{14}H_{15}N_2OCl$, 262.0873). The sample may be impure.

II. Intermediates

17

C. 4(3H)-Quinazolinones - continued

2. 2-Alkyl-4(3H)-quinazolinones

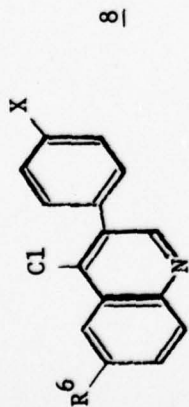
<u>7</u>	<u>R</u>	<u>R⁵</u>	<u>R⁶</u>	<u>R⁷</u>	<u>R⁸</u>	<u>Substituent Identification</u>	<u>mp°</u>	<u>Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>
<u>k</u>	<u>S</u>	H	H	C1	H	7-chloro-2-cyclohexyl	255.5-256	C ₁₄ H ₁₅ N ₂ OC1 262.73	C 64.00 H 5.75 N 10.66 64.00 5.55 10.62	C1 13.50 13.72	GTK
<u>l</u>	<u>S</u>	H	H	H	C1	8-chloro-2-cyclohexyl	241-244	C ₁₄ H ₁₅ N ₂ OC1 262.73	C 64.00 H 5.75 N 10.66 63.78 5.53 10.56	C1 13.50 13.61	GTK

<u>7</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-127	AW 49382	0.5	16/04/70
<u>b</u>	JM-141	AW 49426	0.6	16/04/70
<u>c</u>	JM-131	AW 49417	0.6	16/04/70
<u>d</u>	JM-85	AW 49391	0.6	16/04/70
<u>e</u>	JM-70	AW 49408	0.1	16/04/70
<u>f</u>	JM-135	AW 49453	0.15	16/04/70
<u>g</u>	JM-138	AW 49515	0.6	16/04/70
<u>h</u>	JM-136	AW 49499	0.6	16/04/70
<u>i</u>	JM-110	AW 49435	0.15	16/04/70
<u>j</u>	JM-64	AW 49444	0.6	16/04/70
<u>k</u>	JM-80	AW 49471	0.6	16/04/70
<u>l</u>	JM-97	AW 49506	0.6	16/04/70

<u>7a</u>	mice (07/08/70)	640 T-C 0.3; chick (07/08/70)	120 T-C 0
<u>7b</u>	mice (07/08/70)	640 T-C 0.7	
<u>7c</u>	mice (07/08/70)	640 T-C 0.5	
<u>7d</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70)	160 T-C 0
<u>7e</u>	no report		
<u>7f</u>	mice (07/08/70, 23/09/70)	160 T-C 0.7	
<u>7g</u>	mice (07/08/70)	160 T-C 0.3, 320 T-C 0.9, 3 toxic deaths at 4 days, 640 5 toxic deaths at 4 days (incorrectly listed on printout as the 7-nitro derivative)	
<u>7h</u>	mice (07/08/70)	640 T-C 0.1	
<u>7i</u>	mice (07/08/70, 23/09/70)	160 T-C 0.1; chick (07/08/70)	100 T-C 0
<u>7j</u>	mice (07/08/70)	640 T-C 0.1	
<u>7k</u>	mice (07/08/70)	640 T-C 0.3; chick (07/08/70)	160 T-C 0
<u>7l</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70)	100 T-C 0

II. Intermediates - continued

D. 4-Chloro-3-phenylquinolines



8

8	X	R ⁶	Substituent Identification	mp°	Formula Mol. Wt.	Anal.		Calcd. %		Source or Reference
								Found		
a	OCH ₃	H	3-(4-methoxyphenyl)	92-93 95-96	C ₁₆ H ₁₂ NOC1 269.72	C 71.24 71.21	H 4.49 4.40	N 5.19 4.95	C1 13.15 12.96	MAS
b	CH ₃	H	3-(4-methylphenyl)	71-72	C ₁₆ H ₁₂ NC1 253.72	C 75.74 76.03	H 4.77 4.72	N 5.52 5.60	C1 13.97 13.91	MAS
c	H	H	3-phenyl	72-73 74-75 ^P	C ₁₅ H ₁₀ NC1 239.70	C 75.16 75.4 ^P	H 4.21 4.4 ^P	N 5.84 -	C1 14.79 -	MAS ^P
d	Br	H	3-(4-bromophenyl)	119-121 120-120.5	C ₁₅ H ₉ NBrC1 318.60	C 56.54 56.76	H 2.85 2.88	N 4.40 4.18	C1 22.26* 21.85*	MAS
e	NO ₂	H	3-(4-nitrophenyl)	194-196	C ₁₅ H ₉ N ₂ O ₂ C1 284.70	C 63.28 63.62	H 3.19 3.26	N 9.84 9.75	C1 12.45 12.45	MAS
f	OCH ₃	Cl	6-chloro-3-(4- methoxyphenyl)	158-159 156-167	C ₁₆ H ₁₁ NOC1 ₂ 304.17	C 63.18 63.22	H 3.65 3.68	N 4.60 4.48	C1 23.31 23.14	MAS
g	H	NO ₂	6-nitro-3-phenyl	162-163 167-168	C ₁₅ H ₉ N ₂ O ₂ C1 284.70	C 63.28 64.24	H 3.19 3.59	N 9.84 9.40	C1 12.45 11.98	MAS

*Includes Br as Cl.

II. Intermediates - continued

D. 4-Chloro-3-phenylquinolines

<u>8</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	NS-27	AD 55974	0.5	17/05/68
<u>b</u>	NS-47	AF 52553	0.5	29/10/68
<u>c</u>	NS-5	AD 22699	0.5	01/05/68
<u>d</u>	NS-31	AD 55992	0.5	17/05/68
<u>e</u>	NS-11	AD 22724	0.5	01/05/68
<u>f</u>	NS-52	AF 52599	0.5	29/10/68
<u>g</u>	NS-34	AD 56006	0.5	17/05/68

8a mice (21/08/68) 640 T-C 0.3

8b mice (14/04/69) 640 T-C 1.4

8c mice (31/07/68) 160 T-C 0.7; chick (31/07/68) 320 T-C 0.1; P. gall. A. aegypti (10/10/68) 0.1% 9% toxic deaths (control 3%) 25% sporozoite suppression (control 0%), 0.1% 3% toxic deaths (control 6%) neg. (thus, not confirming the previous run)

8d mice (21/08/68) 640 T-C 0.1

8e mice (31/07/68) 640 T-C 0.3; P. gall. A. aegypti (26/06/69) 0.1% 100% toxic deaths (control 23%) 50% oocyst suppression (control 0%) otherwise neg.

8f mice (14/04/69) 640 T-C 1.8

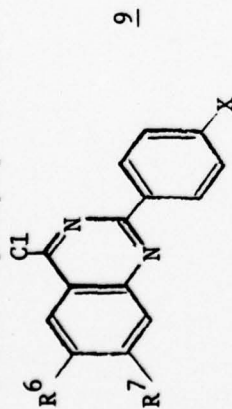
8g mice (21/08/68) 640 T-C 0.1

II. Intermediates - continued

20

E. 4-Chloroquinazolines

1. 4-Chloro-2-phenylquinazolines



<u>9</u>	<u>X</u>	<u>R⁶</u>	<u>R⁷</u>	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
<u>a</u>	OCH ₃	H	H	2-(4-methoxy-phenyl)	121-122	C ₁₅ H ₁₁ N ₂ OCl 270.71	H 4.09 4.00	N 10.35 10.10 C1 13.10 12.92	MAS
<u>b</u>	H	H	H	2-phenyl	128-129 127.5-128.5 124-124.5 ^a 127-128 ^q	C ₁₄ H ₉ N ₂ Cl 240.68	H 3.77 4.16 3.95 ^a 3.74 ^q	N 11.64 11.84 - 11.34 ^q 14.56 ^a 14.88 ^a	MAS ^{a,q} KTK
<u>c</u>	H	Cl	H	6-chloro-2-phenyl	159.5-160 157-159	C ₁₄ H ₈ N ₂ Cl ₂ 275.13	H 2.93 2.92	N 10.18 10.16 C1 25.78 25.38	KTK
<u>d</u>	H	H	Cl	7-chloro-2-phenyl	240-265	C ₁₄ H ₈ N ₂ Cl ₂ [*] 275.13	H 2.93 - - -	N 10.18 - - - C1 25.78 -	KTK

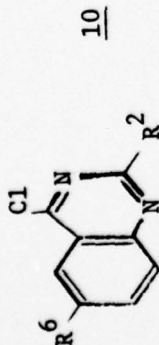
<u>9</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>	
<u>a</u>	NS-84	AU 24938	0.5	28/05/69	<u>9a</u> no report
<u>b</u>	NS-79 JM-24	AU 24910 AW 49551	0.5 0.5	28/05/69 16/04/70	<u>9b</u> mice (05/11/69) 640 T-C 0.3 (07/08/70) 640 T-C 0.3; chick (07/08/70) 160 T-C 0
<u>c</u>	JM-4-A JM-11E (JM-11)	WR-93217-A AW 49917	0.504 0.35	14/12/67 23/04/70	<u>9c</u> mice (04/04/68) 640 T-C 0.2
<u>d</u>	JM-121	AW 49588	0.6	16/04/70	<u>9d</u> mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0


*High resolution mass spectrum m/e (rel intensity) 274.0057 (36), 274.0038 (39) (M⁺, calcd for C₁₄H₈N₂Cl₂, 274.0065); 239.0425 (100), 239.0370 (100) [(M - Cl)⁺, calcd for C₁₄H₈N₂Cl, 239.0377].

II. Intermediates

E. 4-Chloroquinazolines - continued

2. 2-Alkyl-4-chloroquinazolines

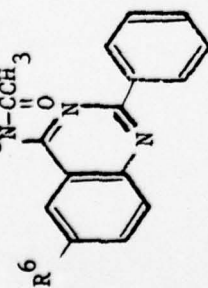
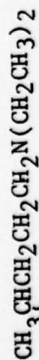


<u>10</u>	<u>R²</u>	<u>R⁶</u>	<u>Substituent</u> <u>Identification</u>	<u>mp°</u>	<u>Formula</u> <u>Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. %</u> <u>Found</u>	<u>Source or</u> <u>Reference</u>
<u>a</u>	CCl ₃	H	2-trichloromethyl	127-128.5	C ₉ H ₄ N ₂ Cl ₄ 281.97	C 38.33 38.14	H 1.43 1.40 N 9.94 9.77 Cl 50.30 50.54	KTK
<u>b</u>		Cl	6-chloro-2-cyclohexyl*	108-128	C ₁₄ H ₁₄ N ₂ Cl ₂ * 281.18	C 59.80	H 5.02 N 9.96 Cl 25.22	KTK
<u>10</u>	<u>Our No.</u>	<u>Walter</u> <u>Reed No.</u>	<u>Sample</u> <u>Size, g.</u>	<u>Date</u> <u>Received</u>				
<u>a</u>	JM-132	AW 49560	0.6	16/04/70	<u>10a</u>	mice (07/08/70)	640 T-C 0.3	
<u>b</u>	JM-72	AW 49579	0.2	16/04/70	<u>10b</u>	mice (07/08/70, 23/09/70) chick (07/08/70)	160 T-C 0.3; 120 T-C 0	

*The structure and molecular formula are not confirmed by high resolution mass spectrometry. Many higher mass peaks are observed, the highest significant being a complex of isotopic peaks about m/e (rel intensity) 351.1483 (36, calcd for C₂₁H₂₂N₃Cl, 351.1503), with the base peak at 296.0942 (100, calcd for C₁₇H₁₅N₃Cl, 296.0955). The peak in the 280 region, at 280.0604 (6) may correspond to C₁₆H₁₁N₃Cl (calcd 280.0622).

II. Intermediates - continued

F. N-(4-Diethylamino-1-methylbutyl)-N-(2-phenylquinazolin-4-yl)acetamides



11

<u>11</u>	<u>R</u>	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
<u>a</u>	H	2-phenyl*	127.5-128.5	C ₂₅ H ₃₂ N ₄ O* 404.54	C 74.22 H 7.97 N 13.85		GTK
<u>b</u>	Cl	6-chloro-2-phenyl ¹	161.5-165	C ₂₅ H ₃₁ N ₄ OCl [#] 438.99	C 68.40 H 7.12 N 12.76 Cl 8.08		GTK

<u>11</u>	Our No.	Walter Reed No.	Sample Size, g.	Date Received
<u>a</u>	JM-23	AW 49748	0.7	16/04/70
<u>b</u>	JM-21	AW 49757	0.2	16/04/70

11a mice (07/08/70) 640 T-C 3.9

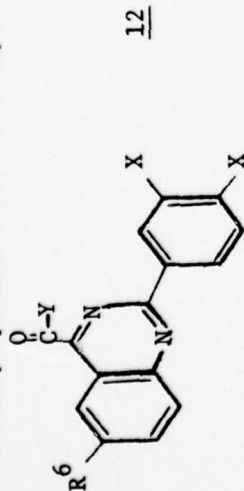
11b mice (07/08/70, 23/09/70) 160 T-C 0.1

*This compound almost certainly does not have the structure 11a shown (on the data sheet, the 4-substituent is shown, incorrectly, as CH₃CONH-). The melting point, but not the biological test data, corresponds to that of 9b, a synthetic precursor of structure 11a. A sample, mp 244.5°, of another product from the reaction was shown by high resolution mass spectrometry to be 6b, a synthetic precursor of and also a hydrolysis product of 9b. Mass spectrum of 6b m/e (rel intensity) 222.0787 [M⁺ (60)], calcd. for C₁₄H₁₀N₂O, 222.0793], 119.0375 [(M - C₇H₅N)⁺ (100), calcd for C₇H₅NO, 119.0371], 77.0350 [(M - C₈H₅N₂O)⁺ (18), calcd for C₆H₅, 77.0391].

#The structure and molecular formula are not confirmed by high resolution mass spectrometry. There are no peaks of mass as high (438) as the proposed molecular ion. The base peak corresponds to a fragment, CH₂=N(CH₂CH₃)₂, derivable from the hypothetical sidechain; mass spectrum m/e (rel intensity) 86.0952 (100, calcd. for C₅H₁₂N, 86.0969).

G. Quinazoline-4-carboxylic Acids and Derivatives

1. 2-Phenylquinazoline-4-carboxylic Acids and Derivatives





<u>12</u>	<u>X</u>	<u>R⁶</u>	<u>Y</u>	<u>Substituent Identification</u>	<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>
<u>a</u>	H	H	OCH ₃	2-phenyl, methyl ester	100-112	C ₁₆ H ₁₂ N ₂ O ₂ 268.30	C 71.62 H 6.01 N 10.44	-	GTK
<u>b</u>	H	H	OC ₆ H ₅	2-phenyl, phenyl ester	130-131	C ₂₁ H ₁₄ N ₂ O ₂ 326.34	C 77.28 H 4.32 N 8.58	-	GTK
<u>c</u>	H	H	Cl	2-phenyl, acid chloride*	88-91	C ₁₅ H ₉ N ₂ OCl* 268.70	C 67.04 H 3.38 N 10.43	Cl 13.20	GTK
<u>d</u>	Cl	H	ONa	2-(3,4-di-chlorophenyl), sodium salt	>370	C ₁₅ H ₇ N ₂ O ₂ NaCl ₂ 341.13	C 52.81 H 2.07 N 8.21	Cl 20.79	GTK
<u>e</u>	Cl	H	NH ₂	2-(3,4-di-chlorophenyl), amide	278-279	C ₁₅ H ₉ N ₃ OCl ₂ 318.16	C 56.62 H 2.85 N 13.21	Cl 22.29	GTK
<u>f</u>	Cl	Cl	OH	6-chloro-2-(3,4-dichloro-phenyl), acid	281-286	C ₁₅ H ₇ N ₂ O ₂ Cl ₃ 353.59	56.20 3.25 13.21 54.90 2.59 11.51	21.83	GTK
<u>g</u>	Cl	Cl	OLi	6-chloro-2-(3,4-dichloro-phenyl), lithium salt	183	C ₁₅ H ₆ N ₂ O ₂ LiCl ₃ 359.52	C 50.95 H 2.00 N 7.92	Cl 30.08 29.96	GTK
<u>h</u>	Cl	Cl	ONa	6-chloro-2-(3,4-dichloro-phenyl), sodium salt	224-226	C ₁₅ H ₆ N ₂ O ₂ NaCl ₃ 375.58	C 50.11 H 1.68 N 7.79	Cl 29.59	GTK
	Cl	Cl	ONa	6-chloro-2-(3,4-dichloro-phenyl), sodium salt	155-160 dec	C ₁₅ H ₆ N ₂ O ₂ NaCl ₃ 375.58	C 47.97 H 1.61 N 7.46	Cl 28.32	GTK

*High resolution mass spectrometry on an eight-year old sample gave no peak of mass quite as high as the expected molecular ion. There was a peak at m/e 250 which may correspond to the hydrolysis product of 12c, the corresponding carboxylic acid, C₁₅H₁₀N₂O₂. The base peak corresponds to the decarboxylation product, C₁₄H₉N₂; mass spectrum m/e (rel intensity) 250.0790 [M⁺(9), calcd for C₁₅H₁₀N₂O₂, 250.0742], 206.0863 [(M-CO₂)⁺(100), calcd for C₁₄H₉N₂, 206.0863], 205.0786 [(M-CO₂H)⁺(38), calcd for C₁₄H₉N₂, 205.0766], 179.0733 [(M-NCCOOH)⁺(36), calcd for C₁₃H₉N, 179.0735]. The peak at m/e 205.0786 could also correspond to the loss of COCl from 12c.

G. Quinazoline-4-carboxylic Acids and Derivatives

1. 2-Phenylquinazoline-4-carboxylic Acids and Derivatives - continued

12	X	R ⁶	Y	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
<u>i</u>	C1	C1	OCH ₃	6-chloro-2-(3,4-dichlorophenyl), methyl ester	193-193.5 192-193	C ₁₆ H ₉ N ₂ O ₂ Cl ₃ 367.62	C 52.27 H 2.47 N 7.62 52.21 2.34 7.12	C1 28.94 29.31	GTK
<u>j</u>	C1	C1	-O-  -NO ₂	6-chloro-2-(3,4-dichlorophenyl), 4-nitrophenyl ester [#]	275-277	C ₂₁ N ₁₀ N ₃ O ₄ Cl ₃ 474.68	C 53.13 H 2.12 N 8.85	C1 22.41	GTK
<u>k</u>	C1	C1	Cl	6-chloro-2-(3,4-dichlorophenyl), acid chloride	190-195	C ₁₅ H ₆ N ₂ OCl ₄ 372.04	C 48.42 H 1.63 N 7.53	C1 38.12	GTK
<u>l</u>	C1	C1	NH ₂	6-chloro-2-(3,4-dichlorophenyl), amide	303-304	C ₁₅ H ₈ N ₃ OCl ₃ 352.61	C 51.09 H 2.29 N 11.92 51.17 2.38 12.18	C1 30.16	GTK
<u>m</u>	C1	C1		6-chloro-2-(3,4-dichlorophenyl), 2-pyridyl ketone ⁺	205-230	C ₂₀ H ₁₀ N ₃ OCl ₃ 414.68	C 57.93 H 2.43 N 10.13 50.67 2.29 12.07	C1 25.65	GTK

12	Our No.	Walter Reed No.	Sample Size, g.	Date Received
<u>a</u>	JM-182	AW 49640	0.15	16/04/70
<u>b</u>	JM-185 (JM-187)	AW 98518	0.2	16/04/70
<u>c</u>	JM-181	AW 49711	0.3	16/04/70
<u>d</u>	JM-168	AW 49613	0.6	16/04/70
<u>e</u>	JM-166	AW 49702	0.6	16/04/70
<u>f</u>	JM-178	AW 49604	0.3	16/04/70
<u>g</u>	JM-195	AW 49631	0.3	16/04/70
<u>h</u>	JM-177	AW 49622	0.6	16/04/70
<u>i</u>	JM-179	AW 49659	0.6	16/04/70
<u>j</u>	JM-188	AW 49688	0.6	16/04/70
<u>k</u>	JM-183	AW 49720	0.1	16/04/70
<u>l</u>	JM-176	AW 49686	0.3	16/04/70
<u>m</u>	JM-180	AW 49739	0.6	16/04/70

[#]The structure and molecular formula are not confirmed by low resolution mass spectrometry, although isotopic clusters may be consistent with the presence of chlorine. There is no molecular ion peak at 473. The highest significant mass peaks are at m/e (rel intensity) 382 (0.4) and 384 (0.4) with very few peaks having much intensity, except at 139 (5), 101 (43), 100 (16), and 87 (15), before the base peak at 86 (100).

⁺Footnote is on next page.

12a mice (07/08/70, 23/09/70) 160 T-C 0.1
12b mice (23/09/70) 160 T-C 0.1; chick (10/02/71) 100 T-C 0
12c mice (07/08/70, 23/09/70) 320 T-C 0.5
12d mice (07/08/70) 640 T-C 0.7; chick (07/08/70) 160 T-C 0
12e mice (07/08/70) 640 T-C 0.1
12f mice (07/08/70, 23/09/70) 320 T-C 0.3; chick (07/08/70) 120 T-C 0
12g mice (07/08/70, 23/09/70) 320 T-C 0.3; chick (07/08/70) 120 T-C 0
12h mice (07/08/70) 640 T-C 2.9
12i mice (07/08/70) 640 T-C 2.5; chick (07/08/70) 160 T-C 0
12j mice (07/08/70) 640 T-C 0.3; chick (07/08/70) 160 T-C 0
12k mice (07/08/70, 23/09/70) 80 T-C 0.1
12l mice (07/08/70, 23/09/70) 320 T-C 0.3; chick (07/08/70) 120 T-C 0
12m mice (07/08/70) 640 T-C 0.3

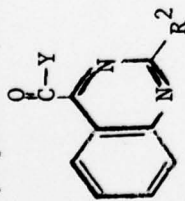
†The structure and molecular formula are not confirmed by low resolution mass spectrometry. There is no molecular ion peak at 413. The highest mass peak is at m/e (rel intensity) 391 (0.2) with very few peaks having much intensity, except at 387 (5), 385 (6), 256 (12), 160 (14), 128 (12), and 66 (9), before the base peak at 64 (100).

II. Intermediates

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G. Quinazoline-4-carboxylic Acids and Derivatives - continued

2. 2-Alkylquinazoline-4-carboxylic Acids and Amides



<u>13</u>	<u>R³</u>	<u>Y</u>	<u>Substituent Identification</u>	<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>
<u>a</u>	CH ₃	OH	2-methyl, acid	191-192	C ₁₀ H ₈ N ₂ O ₂ 188.18	C 63.82 H 4.29 N 14.89	- - -	GTK
<u>b</u>	CH ₃	NH ₂	2-methyl, amide	172-176.5	C ₁₀ H ₉ N ₃ O 187.20	C 64.16 H 4.85 N 22.45	- - -	GTK
<u>c</u>	CF ₃	NH ₂	2-trifluoromethyl, amide*	255-263	C ₁₀ H ₆ N ₃ OF ₃ 241.17	C 49.80 H 2.51 N 17.43	- - -	GTK

<u>13</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-160	AW 49597	0.6	16/04/70
<u>b</u>	JM-158	AW 49677	0.6	16/04/70
<u>c</u>	JM-162	AW 49695	0.5	16/04/70

13a mice (07/08/70) 640 T-C 0.1

13b mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 120 T-C 0

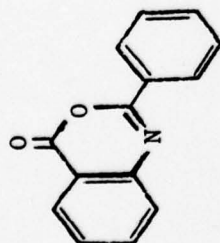
13c mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 120 T-C 0

*The structure and molecular formula are not confirmed by high resolution mass spectrometry.

II. Intermediates - continued

H. 4(4H)-3,1-Benzoxazinones

1. 2-Phenyl-4(4H)-3,1-benzoxazinone



14

mp°	Formula	Mol. Wt.	Anal.	Calcd. % Found	Source or Reference	Our No.	Walter Reed No.	Sample Size, g.	Date Received
116-124	C ₁₄ H ₉ NO ₂	223.22	C 75.32 H 4.06 N 6.28	- - -	GTK	JM-88	AW 49524	0.6	16/04/70

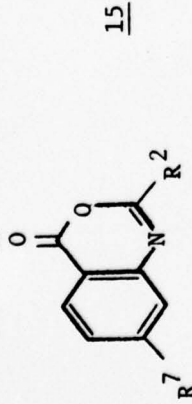
14 mice (07/08/70) 640 T-C 0.1


II. Intermediates

28

H. 4(4H)-3,1-Benzoxazinones - continued

2. 2-Alkyl-4(4H)-3,1-benzoxazinones



15	R ²	R ⁷	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
a	CF ₃	H	2-trifluoromethyl*	180-181	C ₉ H ₄ NO ₂ F ₃ [*] 215.13	C 50.24 H 1.87 N 6.51	-	KTK
b		Cl	7-chloro-2-cyclohexyl [#]	200-215	C ₁₄ H ₁₄ NO ₂ Cl [#] 263.72	C 63.76 H 5.35 N 5.31 Cl 13.45	-	KTK

15	Our No.	Walter Reed No.	Sample Size, g.	Date Received
a	JM-144*	AW 49542	0.3	16/04/70
b	JM-82	AW 49533	0.6	16/04/70

15a mice (07/08/70, 23/09/70) 320 T-C 0.3

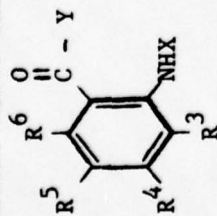
15b mice (07/08/70) 640 T-C 0.3; chick (07/08/70) 120 T-C 0

*There are two compounds with our no. JM-144, 15a (AW 49542) and 17b (AW 49168), but they can be distinguished by their Walter Reed nos. This sample does not have the structure shown but is identical with compound 17b, as shown by comparison of the infrared spectra in Nujol, and by the high resolution mass spectrum m/e (rel intensity) 233.0317 [M⁺(33), calcd for C₉H₄NO₂F₃⁺, 215.0181 [(M-H₂O)⁺ or M⁺ of 15a (11), calcd for C₉H₄NO₂F₃⁺, 215.0194], 146.0172 [(M-HCF₃-OH)⁺ (146), calcd for C₈H₄NO₂, 146.0242], 90.0341 [(M-C₃H₂O₃F₃)⁺ (44), calcd for C₆H₄N, 90.0344].

[#]This sample appears to be a mixture, probably containing considerably more of the precursor 17e than of 15b, as judged from the high resolution mass spectrum m/e (rel intensity for m/e > 206 only) 283.0834 [M(37Cl)⁺ for 17e (31), calcd for C₁₄H₁₆NO₃³⁷Cl, 283.0789], 281.0816 [M⁺ for 17e (100), calcd for C₁₄H₁₆NO₃³⁵Cl, 281.0819], 263.0711 [M⁺ for 15b (5), calcd for C₁₄H₁₄NO₂Cl, 263.0712].

II. Intermediates - continued

I. Anthranilic Acids and Derivatives



16

	Substituent Identification					mp°	Formula * Mol. Wt.	Calcd. %		Source or Reference
	16	3	4	5	6			Anal.	Found	
a	C1	H	H	H	H	187-192 dec	C ₇ H ₅ NOCl	C 54.39 H 3.26	N 9.06 Cl 22.94	KTK
b	C1	H	H	H	H ₂ Cl	198-199.5 3-chloro, hydrochloride	C ₇ H ₇ NOCl ₂ 154.58	C 43.78 H 3.67	N 7.29 Cl 36.93	KTK
c	H	Cl	H	H	H ₂ Cl	241-242.5 4-chloro, hydrochloride	C ₇ H ₇ NOCl ₂ 192.05	C 43.78 H 3.67	N 7.29 Cl 36.93	KTK
d	H	Cl	H	H	H	68-70 4-chloro, methyl ester	C ₈ H ₈ NO ₂ Cl 185.61	C 51.76 H 4.35	N 7.55 Cl 19.10	KTK
e	H	H	Cl	H	H	213.5-217 5-chloro	C ₇ H ₅ NOCl 154.58	C 54.39 H 3.26	N 9.06 Cl 22.94	KTK
f	H	H	H	Cl	H	63.5-65.5 5-chloro, methyl ester	C ₈ H ₈ NO ₂ Cl 185.61	C 51.76 H 4.35	N 7.55 Cl 19.10	KTK
g	H	H	H	H	Cl	150-151.5 6-chloro	C ₇ H ₅ NOCl 154.58	C 54.39 H 3.26	N 9.06 Cl 22.94	KTK
h	H	H	H	H	Cl	160-178 dec 6-chloro, hydrochloride	C ₇ H ₇ NOCl ₂ 192.05	C 43.78 H 3.67	N 7.29 Cl 36.93	KTK

* Mass spectral data are reported on the next page.

* Mass spectral data:

- 16a** Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl)⁺ (15)], 171 [(M³⁵Cl)⁺ (47)], 155 [(M³⁷Cl - H₂O)⁺ (32)], 154 (10), 153 [(M³⁵Cl - H₂O)⁺ (100)], 127 [(M³⁷Cl - HCOOH)⁺ (10)], 126 [(M - ³⁵Cl - COOH)⁺ (11)], 125 [(M³⁵Cl - HCOOH)⁺ (27)], 118 [(M - H₂O - Cl)⁺ (16)], 90 [(M - HCOOH - Cl)⁺ (33)].
- 16b** Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl - HCl)⁺ (16)], 171 [(M³⁵Cl - HCl)⁺ (50)], 155 [(M³⁷Cl - HCl - H₂O)⁺ (33)], 154 (10), 153 [(M³⁵Cl - HCl - H₂O)⁺ (100)], 127 [(M³⁷Cl - HCl - HCOOH)⁺ (9)], 126 [(M³⁵Cl - HCl - COOH)⁺ (9)], 125 [(M³⁵Cl - HCl - HCOOH)⁺ (23)], 118 [(M - HCl - H₂O - Cl)⁺ (14)], 90 [(M - HCl - COOH - Cl)⁺ (26)]; high resolution mass spectrum m/e (rel intensity) 173.0058 [(M - HCl)⁺ (16), calcd for C₇H₈NO₃Cl, 173.0057], 171.0091 [(M - HCl)⁺ (48), calcd for C₇H₆NO₃Cl, 171.0087], 154.0028 [(M - HCl - H₂O)⁺ (11), calcd for ¹³C₁₂C₇H₈NO₃Cl, 154.0015], 152.9997 [(M - HCl - H₂O)⁺ (100), calcd for C₇H₄NO₃Cl, 152.9981], 125.0030 [(M - HCl - HCOOH)⁺ (22), calcd for C₇H₄N³⁵Cl, 125.0032], 118.0288 [(M - HCl - H₂O - Cl)⁺ (13), calcd for C₇H₄NO, 118.0293], 90.0350 [(M - HCl - COOH - Cl)⁺ (20), calcd for C₆H₄N, 90.0344].
- 16c** Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl - HCl)⁺ (18)], 171 [(M³⁵Cl - HCl)⁺ (56)], 155 [(M³⁷Cl - HCl - H₂O)⁺ (33)], 154 (13), 153 [(M³⁵Cl - HCl - H₂O)⁺ (100)], 128 [(M³⁷Cl - HCl - COOH)⁺ (16)], 126 [(M³⁵Cl - HCl - COOH)⁺ (49)], 90 [(M - HCl - COOH - Cl)⁺ (11)].
- 16d** Low resolution mass spectrum m/e (rel intensity) 187 [(M³⁷Cl)⁺ (19)], 185 [(M³⁵Cl)⁺ (58)], 156 [(M³⁷Cl - CH₃O)⁺ (12)], 155 [(M³⁷Cl - CH₃OH)⁺ (35)], 154 [(M³⁵Cl - CH₃O)⁺ (38)], 153 [(M³⁵Cl - CH₃OH)⁺ (100)], 128 [(M³⁷Cl - COOH)⁺ (14)], 126 [(M³⁵Cl - COOH)⁺ (44)], 99 [(M³⁵Cl - COOH - HCN)⁺ (13)], 90 [(M³⁵Cl - HCOOH - Cl)⁺ (90)]; high resolution mass spectrum m/e (rel intensity) 187.0214 [M⁺ (18), calcd for C₈H₈N₂O³⁷Cl, 187.0214], 185.0252 [M⁺ (54), calcd for C₈H₈NO₃Cl, 185.0243], 156.0035 [(M - CH₃O)⁺ (11), calcd for C₇H₈NO³⁷Cl, 156.0030], 154.9979 [(M - CH₃OH)⁺ (40), calcd for C₇H₈NO³⁷Cl, 154.9952], 154.0069 [(M - CH₃O)⁺ (38), calcd for C₇H₈NO³⁵Cl, 154.0060], 153.0002 [(M - CH₃OH)⁺ (100), calcd for C₇H₈NO³⁵Cl, 152.9981], 127.9923 [(M - COOH)⁺ (14), calcd for C₇H₈N³⁷Cl, 128.0488], 125.9860 [(M - COOH)⁺ (27), calcd for C₇H₈N³⁵Cl, 126.0111], 99.0004 [(M - COOH - HCN)⁺ (11), calcd for C₅H₄³⁵Cl, 99.0001], 90.0317 [(M - HCOOH - Cl)⁺ (12), calcd for C₆H₄N, 90.0344].
- 16e** Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl)⁺ (16)], 171 [(M³⁵Cl)⁺ (52)], 155 [(M³⁷Cl - H₂O)⁺ (32)], 153 [(M³⁵Cl - H₂O)⁺ (100)], 127 [(M³⁷Cl - HCOOH)⁺ (12)], 126 [(M³⁵Cl - COOH)⁺ (23)], 125 [(M³⁵Cl - HCOOH)⁺ (28)], 90 [(M - HCOOH - Cl)⁺ (12)].
- 16f** The low resolution mass spectrum suggests that the sample at time of analysis (8 1/2 years later) was quite impure; m/e (rel intensity) 185 [M⁺ (100)].
- 16g** Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl)⁺ (17)], 171 [(M³⁵Cl)⁺ (52)], 155 [(M³⁷Cl - H₂O)⁺ (33)], 154 (11), 153 [(M³⁵Cl - H₂O)⁺ (100)], 128 [(M³⁷Cl - COOH)⁺ (15)], 126 [(M³⁵Cl - COOH)⁺ (47)], 90 [(M - HCOOH - Cl)⁺ (17)].
- 16h** Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl - HCl)⁺ (14)], 171 [(M³⁵Cl - HCl)⁺ (44)], 155 [(M³⁷Cl - HCl - H₂O)⁺ (32)], 154 (10), 153 [(M³⁵Cl - HCl - H₂O)⁺ (100)], 128 [(M³⁷Cl - HCl - COOH)⁺ (18)], 126 [(M³⁵Cl - HCl - COOH)⁺ (56)], 90 [(M - HCl - HCOOH - Cl)⁺ (24)].

II. Intermediates - continued

I. Anthranilic Acids and Derivatives

<u>16</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-119	AW 98527	0.6	16/04/70
<u>b</u>	JM-95	AW 49195	0.2	16/04/70
<u>c</u>	JM-109	AW 49211	0.1	16/04/70
<u>d</u>	JM-77	AW 49239	0.6	16/04/70
<u>e</u>	JM-55B	AW 49202	0.6	16/04/70
<u>f</u>	JM-50	AW 49220	0.6	16/04/70
<u>g</u>	JM-122	AW 49177	0.6	16/04/70
<u>h</u>	JM-108	AW 49186	0.7	16/04/70

16a mice (23/09/70) 640 T-C 0.3; chick (10/02/71) 160 T-C 0

16b mice (23/09/70) 320 T-C 0.7

16c mice (23/09/70) 80 T-C 3.1

16d mice (07/08/70) 640 T-C 0.5

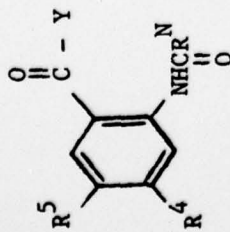
16e mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0

16f mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0

16g mice (07/08/70) 640 T-C 2.3; chick (07/08/70) 160 T-C 0

16h mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0

J. N-Acylanthranilic Acids and Derivatives



17

17	R ^N	R ⁴	R ⁵	Y	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
a	CH ₃	H	H	OH	N-acetyl	191-192.5	C ₉ H ₉ NO ₃ 179.17	C 60.33 H 5.06 N 7.82	-	KTK
b	CF ₃	H	H	OH	N-trifluoroacetyl	188-190	C ₉ H ₆ NO ₃ F ₃ 233.15	C 46.36 H 2.59 N 6.01 46.48 2.67 5.94 45.87 2.60 5.92	-	KTK
c		H	H	OH	N-cyclohexane-carbonyl*	178-180 231-232	C ₁₄ H ₁₇ NO ₃ * 247.28	C 67.99 H 6.93 N 5.66 68.41 6.01 7.42 68.89 5.82 7.66	-	KTK
d		H	H	OH	N-(4-nitrobenzoyl)*	272-275	C ₁₄ H ₁₀ N ₂ O ₅ * 286.24	C 58.74 H 3.52 N 9.79	-	KTK
e		Cl	H	OH	4-chloro-N-cyclohexanecarbonyl	233-234.5	C ₁₄ H ₁₆ NO ₃ Cl 281.73	C 59.68 H 5.72 N 4.97 59.48 5.56 4.92	Cl 12.59 12.76	KTK
f		Cl	H	OCH ₃	4-chloro-N-cyclohexanecarbonyl, methyl ester	135.5-136	C ₁₅ H ₁₈ NO ₃ Cl 295.76	C 60.91 H 6.13 N 4.74 60.93 6.11 4.62	Cl 11.99 12.09	KTK
g		H	Cl	OCH ₃	5-chloro-N-cyclohexanecarbonyl, methyl ester	143.5-144	C ₁₅ H ₁₈ NO ₃ Cl 295.76	C 60.91 H 6.13 N 4.74 61.20 6.11 4.64	Cl 11.99 12.08	KTK
h		H	Cl	OH	5-chloro-N-(4-nitrobenzoyl)	291-293	C ₁₄ H ₉ N ₂ O ₅ Cl* 320.68	C 52.43 H 2.83 N 8.74 52.86 3.73 9.88	Cl 11.05 13.04	KTK
i		H	Cl	OCH ₃	5-chloro-N-(4-nitrobenzoyl), methyl ester	264-267	C ₁₅ H ₁₁ N ₂ O ₅ Cl* 334.71	C 53.82 H 3.31 N 8.37 52.35 2.98 8.28	Cl 10.59 12.70	KTK
j		H	Cl	NH ₂	5-chloro-N-(4-nitrobenzoyl), amide*	294-302 268.5-270	C ₁₄ H ₁₀ N ₃ O ₄ Cl* 319.70	C 52.59 H 3.15 N 13.15 51.42 3.21 9.32*	Cl 11.09 10.12	KTK
k		H	NO ₂	OH*#	5-nitro-N-(4-nitrobenzoyl)*#	270-284.5	C ₁₄ H ₉ N ₃ O ₇ * 331.24	C 50.76 H 2.74 N 12.69	-	KTK

(footnotes are on next page)

17c After 8 2/3 years, the sample appeared to have partially decomposed, as indicated by the appearance of brown specks. From the high resolution mass spectrum, the compound appears to be a mixture with a significant peak at 265 but not corresponding to $C_{14}H_{19}NO_4$ (the salt of anthranilic acid and cyclohexanecarboxylic acid), no molecular ion peak at 247 corresponding to 17c but a significant peak at 230 corresponding to loss of hydroxyl from 17c, a base peak at 137 corresponding to the molecular ion of anthranilic acid (also a possible fragmentation product of 17c), and a significant peak at 120 corresponding to the loss of hydroxyl from anthranilic acid (or of cyclohexanecarboxylate from 17c; m/e 265.0632 (33), 230.1192 [(M - OH)⁺ (52), calcd for $C_{14}H_{16}NO_2$, 230.1181], 137.0515 [(M - $C_6H_{11}CO + H$)⁺ (100), calcd for $C_7H_7NO_2$, 137.0477], 120.0446 [(M - $C_6H_{11}COO$)⁺ (57), calcd for C_7H_6NO , 120.0449].

17d The structure and molecular formula are not confirmed by low resolution mass spectrometry. The sample appears to contain a mixture of 4-nitrobenzoic acid (the base peak at 167 corresponds to the molecular ion) and anthranilic acid (a major peak at 137 corresponds to the molecular ion), or a salt of the two. Major peaks occur at m/e (rel intensity) 167 (100, $O_2NC_6H_4COOH^+$), 137 (26, $H_2NC_6H_4COOH^+$), 121 (43, $C_6H_4COOH^+$), 109 (17), 73 (78, C_6H^+), 65 (51), 44 (27, CO_2^+).

17h Low resolution mass spectrum m/e (rel intensity) 304 [(M³⁷Cl - H₂O)⁺ (6)], 302 [(M³⁵Cl - H₂O)⁺ (17)], 272 (10), 187 (12), 185 (29), 173 [(C₇H₆NO₂³⁷Cl)⁺ (16)], 171 [(C₇H₆NO₂³⁵Cl)⁺ (30)], 156 (19), 155 [(C₇H₆NO³⁷Cl)⁺ (38)], 154 (63), 153 [(C₇H₆NO³⁵Cl)⁺ (100)], 150 (17), 128 [(C₆H₅N³⁷Cl)⁺ (19)], 127 [(C₆H₅N³⁷Cl)⁺ (22)], 126 [(C₆H₅N³⁵Cl)⁺ (51)], 125 [(C₆H₅N³⁵Cl)⁺ (36)], 120 [(C₆H₅NO)⁺ (77)], 98 (25), 92 (19), 91 (10), 90 [(C₆H₅N)⁺ (38)], 89 (33); high resolution mass spectrum m/e (rel intensity) 304.0030 [(M - H₂O)⁺ (15), calcd for $C_{14}H_{16}NO_2^{37}Cl$, 304.0065], 302.0058 [(M - H₂O)⁺ (55), calcd for $C_{14}H_{16}NO_2^{35}Cl$, 302.0094], 173.0071 [(15), calcd for $C_{14}H_{16}NO_2^{37}Cl$, 173.0057], 171.0096 [(46), calcd for $C_7H_6NO_2^{35}Cl$, 171.0087], 154.9842 [(45), calcd for $C_7H_4NO_2^{37}Cl$, 154.9952], 153.9896 [(12), calcd for $C_7H_5NO_2^{35}Cl$, 154.0060], 152.9830 [(100), calcd for $C_7H_4NO_2^{35}Cl$, 152.9981]; on another spectrum: 305.0103 [(M - OH)⁺ (12), calcd for $C_{14}H_{16}NO_2O_4^{37}Cl$, 305.0143], 303.0155 [(M - OH)⁺ (9), calcd for $C_{14}H_{16}NO_2O_4^{35}Cl$, 303.0172], 302.0124 [(M - H₂O)⁺ (24), calcd for $C_{14}H_{16}NO_2O_4^{35}Cl$, 302.0094], 173.0052 [(30), calcd for $C_7H_6NO_2^{37}Cl$, 173.0057], 171.0109 [(67), calcd for $C_7H_6NO_2^{35}Cl$, 171.0087], 152.9975 [(100), calcd for $C_7H_4NO_2^{35}Cl$, 152.9981], 125.0037 [(54), calcd for $C_6H_4N^{35}Cl$, 125.0032], 120.0461 [(70), calcd for C_7H_6NO , 120.0449], 120.0210 [(11), calcd for $C_7H_4O_2$, 120.0211].

(footnotes continued on next page)

* Mass spectral data:

17i Low resolution mass spectrum m/e (rel intensity) 336 [(M³⁷Cl)⁺ (2)], 334 [(M³⁵Cl)⁺ (8)], 322 [(M³⁷Cl - CH₂)⁺ (5)], 320 [(M³⁵Cl - CH₂)⁺ (15)], 304 [(M³⁷Cl - CH₃OH)⁺ (6)], 302 [(M³⁵Cl - CH₃OH)⁺ (18)], 155 [(C₇H₄NO₃Cl)⁺ (9)], 153 [(C₇H₄NO₃Cl)⁺ (29)], 151 [(C₇H₅NO₃)⁺ (8)], 150 [(C₇H₄NO₃)⁺ (100)], 120 [(C₇H₆NO)⁺ or (C₇H₄O₂)⁺ (31)], 104 [(C₇H₄O)⁺ (52)], 92 [(C₆H₄O)⁺ (25)]; high resolution mass spectrum m/e (rel intensity) 334.0377 [M⁺ (8), calcd for C₁₅H₁₁N₂O₅Cl, 334.0357], 320.0159 [(M - CH₂)⁺ (9), calcd for C₁₄H₉N₂O₅³⁵Cl, 320.0200]; on another spectrum: 334.0207 [M⁺ (8), calcd for C₁₅H₁₁N₂O₅Cl, 334.0357], 322.0209 [(M - CH₂)⁺ (16), calcd for C₁₄H₉N₂O₅³⁷Cl, 322.0170], 320.0201 [(M - CH₂)⁺ (69), calcd. for C₁₄H₉N₂O₅³⁵Cl, 320.0200].

17j Consistent with the low nitrogen analysis, the low resolution mass spectrum of another sample shows that the sample consists principally of a mixture of the methyl ester starting material (17i, 334) and the acid hydrolysis product (17h, 320) and fragmentation products derivable therefrom: m/e (rel intensity) 334 (7, C₁₅H₁₁N₂O₅Cl, 17i?), 320 (18, C₁₄H₉N₂O₅Cl, 17h?), 302 (12, C₁₄H₇N₂O₄Cl, 17h - H₂O or 17i - CH₃OH, similar to 15?), 153 (34, C₇H₂NOCl?), 150 (100, O₂NC₆H₄CO?), 120 (39, C₇H₄O₂?), 104 (51, C₆H₄CO?).

17k Low resolution mass spectrum m/e (rel intensity) 376 (0.8), 331 (M⁺ 0.1), 286 [(M - COOH)⁺ (19)], 269 [(M - H₂CO₃)⁺ (20)], 268 [(M - COOH - H₂O)⁺ (100)], 224 [(M - CO₂ - HNO₃)⁺ (49)], 178 [(M - CO₂ - HNO₃ - NO₂)⁺ (22)], 167 [C₇H₅NO₄⁺, 58], 150 [C₇H₄NO₃⁺, 68], 146 (50), 121 (39), 120 (26), 119 (43), 104 (66), 92 (33), 90 (39).

Incorrectly given as the methyl ester in the name and structure on the data sheet for this compound.

II. Intermediates - continued

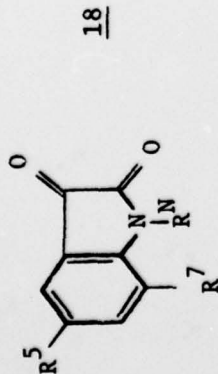
J. N-Acylanthranilic Acids and Derivatives

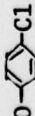


<u>17</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-149	AW 47646	0.6	16/04/70
<u>b</u>	JM-144*	AW 49168	0.4	16/04/70
<u>c</u>	JM-151 (JM-58C)	AW 98509	0.6	16/04/70
<u>d</u>	JM-37 (JM-36-E)	AW 98536	0.4	16/04/70
<u>e</u>	JM-98	AW 49284	0.7	16/04/70
<u>f</u>	JM-79	AW 49293	0.6	16/04/70
<u>g</u>	JM-52	AW 49275	0.6	16/04/70
<u>h</u>	JM-35	AW 49257	0.4	16/04/70
<u>i</u>	JM-41F (JM-41)	AW 49926	0.6	23/04/70
<u>j</u>	JM-39	AW 49266	0.6	16/04/70
<u>k</u>	JM-43	AW 49300	0.6	16/04/70

*There are two samples with our no. JM-144, 15a (AW 49542) and 17b (AW 49168), but they can be distinguished by their Walter Reed nos.

<u>17a</u>	mice (07/08/70)	640 T-C 0.3; chick (07/08/70)	160 T-C 0	<u>17i</u>	mice (07/08/70) 640 T-C 1.1; chick (07/08/70) 160 T-C 0
<u>17b</u>	mice (07/08/70), 23/09/70)	640 T-C 0.3			
<u>17c</u>	mice (23/09/70)	640 T-C 0.3; chick (10/02/71)	160 T-C 0	<u>17j</u>	mice (07/08/70) 640 T-C 0.5; chick (07/08/70) 160 T-C 0
<u>17d</u>	mice (23/09/70)	640 T-C 0.1; chick (10/02/71)	120 T-C 0	<u>17k</u>	mice (07/08/70) 640 T-C 0.5; chick (07/08/70) 160 T-C 0
<u>17e</u>	mice (07/08/70)	640 T-C 0.3			
<u>17f</u>	mice (07/08/70)	640 T-C 0.5; chick (07/08/70)	160 T-C 0		
<u>17g</u>	mice (07/08/70)	640 T-C 0.9			
<u>17h</u>	mice (17/02/72)	320 T-C 0.3			

K. Isatins and Derivatives



18	R ⁵	R ⁷	R ^N	Substituent Identification	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
<u>a</u>	H	H	COCH ₃	N-acetyl	146-147.5	C ₁₀ H ₇ NO ₃	C 63.49 H 3.73	N 7.41	KTK
<u>b</u>	H	H	COCF ₃	N-trifluoroacetyl	163-166	C ₁₀ H ₄ NO ₃ F ₃ [*]	C 49.40 H 1.66	N 5.76	KTK
<u>c</u>	H	H	CO- 	N-(3,4-dichlorobenzoyl)	228-230	C ₁₅ H ₇ NO ₃ Cl ₂	C 56.28 H 2.20	N 4.38 Cl 22.15	KTK
<u>d</u>	Cl	H	Na	5-chloro, sodium salt	-	C ₈ H ₃ NO ₂ NaCl	C 47.20 H 1.48	N 6.88 Cl 17.42	KTK
<u>e</u>	Cl	H	CO- 	5-chloro-N-(3,4-dichlorobenzoyl)	199-200	C ₁₅ H ₆ NO ₃ Cl ₃	C 50.81 H 1.70	N 3.95 Cl 30.00	KTK
<u>f</u>	Cl	Cl	Na	5,7-dichloro, sodium salt	-	C ₈ H ₂ NO ₂ NaCl ₂	C 40.37 H 0.85	N 5.89 Cl 29.79	KTK
<u>g</u>	Cl	Cl	CO- 	5,7-dichloro-N-(3,4-dichlorobenzoyl)	156-158	C ₁₅ H ₅ NO ₃ Cl ₄	C 46.31 H 1.29	N 3.60 Cl 36.46	KTK

* After being kept for 8 1/2 years, the sample of 18b was observed to evolve a gas which fumed in air (trifluoroacetic acid) and to contain a mixture of the original yellow crystals as well as orange crystals (isatin) resulting from partial hydrolysis by atmospheric moisture. The sample was redried under vacuum at room temperature; low resolution mass spectrum m/e (rel intensity) 244 [(M + 1)⁺ 1.5], 243 (M⁺, 9), 215 [(M - CO)⁺ (50)], 147 [(C₈H₅NO₂, isatin)⁺ (16)], 146 [(C₈H₄NO₂, M - COCF₃)⁺ (100)], 119 [(C₇H₅NO, isatin - CO)⁺ (15)], 118 [(C₇H₄NO, M - COCF₃ - CO)⁺ (8)], 92 [(C₆H₆N)⁺ (10)], 91 [(C₆H₅N)⁺ (8)], 90 [(C₆H₄N, M - COCF₃ - 2CO)⁺ (62)]; high resolution mass spectrum m/e (rel intensity) 243.0156 [M⁺ (8), calcd for C₁₀H₄NO₃F₃, 243.0143], 215.0200 [(M - CO)⁺ (38), calcd for C₉H₄NO₂F₃, 215.0194], 147.0305 [(isatin)⁺ (12), calcd for C₈H₅NO₂, 147.0320], 146.0278 [(M - COCF₃)⁺ (100), calcd for C₈H₄NO₂, 146.0242], 90.0361 [(M - COCF₃ - 2CO)⁺ (71), calcd for C₆H₄N, 90.0344]; on another spectrum: 244.0112 [(M + H)⁺ (5), calcd for C₁₀H₅NO₃F₃, 244.0222], 243.0149 [M⁺ (6), calcd for C₁₀H₄NO₃F₃, 243.0143], 215.0147 [(M - CO)⁺ (41), calcd for C₉H₄NO₂F₃, 215.0194], 146.0246 [(M - COCF₃)⁺ (100), calcd for C₈H₄NO₂, 146.0242], 119.0388 [(isatin - CO)⁺ (85), calcd for C₇H₅NO, 119.0371], 118.0252 [(M - COCF₃ - CO)⁺ (11), calcd for C₇H₄NO, 118.0293], 90.0369 [(M - COCF₃ - 2CO)⁺ (46), calcd for C₆H₄N, 90.0344].

II. Intermediates - continued

K. Isatins and Derivatives

<u>18</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-153	AW 49328	0.5	16/04/70
<u>b</u>	JM-156	AW 49319	0.6	16/04/70
<u>c</u>	JM-165	AW 49337	0.2	16/04/70
<u>d</u>	JM-175	AW 49346	0.6	16/04/70
<u>e</u>	JM-170	AW 49355	0.6	16/04/70
<u>f</u>	JM-167	AW 49364	0.6	16/04/70
<u>g</u>	JM-173	AW 49373	0.6	16/04/70

18a mice (07/08/70) 640 T-C 0.1

18b mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0.1

18c mice (07/08/70, 23/09/70) 160 T-C 3.1 and 2.9, 320 5 toxic deaths at 4 days; chick (07/08/70) 100 T-C 0

18d mice (07/08/70) 640 T-C 0.3

18e mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0

18f mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0

18g mice (07/08/70) 640 T-C 0.1

II. Intermediates - continued

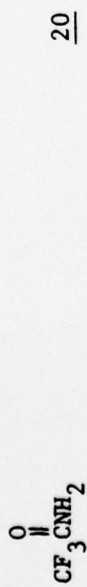
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L. Miscellaneous

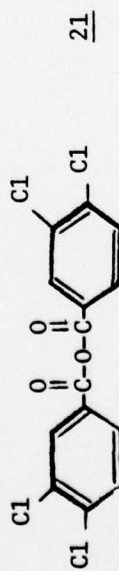
1. 1-Cinnamylpyridinium Chloride



2. Trifluoroacetamide



3. 3,4-Dichlorobenzoic Anhydride



4. 6-Chloro-2-nitrobenzoic Acid



II. Intermediates - continued

39.

L. Miscellaneous

mp°	Formula Mol. Wt.	Anal.		Calcd. % Found		Source or References	Our No.	Walter Reed No.	Sample Size, g.	Date Received
19 33-35	C ₁₄ H ₁₄ NC1 231.72	C 72.56	H 6.09	N 6.05	Cl 15.30	DT	D1	AE 72407	0.5	18/07/68
20 128-129.5	C ₂ H ₂ NOF ₃ * 113.04	C 21.25	H 1.78	N 12.39	Cl -	GTK	JM-140	AW 47628	0.6	16/04/70
21 157-158	C ₁₄ H ₆ O ₃ Cl ₄ 364.02	C 46.19	H 1.66	N -	Cl 38.96	GTK	JM-300	AW 47637	0.5	16/04/70
159-160		45.86	1.72		-					
22 152-163	C ₇ H ₄ NO ₄ Cl ₁ 201.57	C 41.71	H 2.00	N 6.95	Cl 17.59	GTK ^r	JM-99	AW 49248	0.6	16/04/70
161 ^r		-	-	-	-					

19 mice (01/10/68) 80 T-C 0.2, 160 T-C 1.3 but 3 toxic deaths at 4 days, 320 and 640 5 toxic deaths at 3 days; chick (19/11/68) 60 T-C 0.6, 120 T-C 0.8 but 1 toxic death at 1 day, 240 5 toxic deaths at 1 day (06/03/71) 320 5 toxic deaths at 1 day; P. gall. A. aegypti (06/11/68) 0.1% 20% toxic deaths (control 0%) neg.

20 mice (07/08/70) 640 T-C 0.3

21 mice (07/08/70) 640 T-C 0.3

22 mice (07/08/70) 640 T-C 1.3; chick (07/08/70) 160 T-C 0

* Low resolution mass spectrum of 20 m/e (rel intensity) 115 [(CF₃COOH)₂]⁺ (0.2), 114 [(CF₃COOH)₂]⁺ (1.3)], 97 [(CF₃CO)⁺ (8)], 95 [(CF₃CN or CF₂COOH)⁺ (6)], 86 [(CF₃OH)⁺ (1.0)], 69 [(CF₃)⁺ (100)], 51 [(CHF₂)⁺ (40)], 50 [(CF₂)⁺ (15)], 45 [(COOH)⁺ (94)], 44 [(CONH₂)⁺ (10)]; high resolution mass spectrum m/e (rel intensity) 115.0009 [(M + 2)⁺ (0.5), calcd for CF₃COOH₂, 115.006], 113.9938 [(M + 1)⁺ (1.2), calcd for CF₃COOH, 113.9928], 96.9896 [(M - NH₂)⁺ (6), calcd for CF₃CO, 96.9900], 94.9937 [(M - H₂O)⁺ (3.5), calcd for CF₃CN, 94.9983, calcd for CF₂COOH, 94.9944], 85.9972 [(M - CO)⁺ (2.3), calcd for CF₃OH, 85.9979], 68.9910 [(M - CONH₂)⁺ (100), calcd for CF₃, 68.9952].

Sources

MAS = M. Akram Sandhu, postdoctoral research, 1967-69.

KTK = Kung Tu Kuo, postdoctoral research, 1967-69.

TRA = Terence R. Ashe, undergraduate research assistant, 1967-68.

JOB = Jerold O. Bahls, graduate research assistant, U.S. Public Health Service Grant No. 5 R01 CA04073-09,10 "The Reactions of Indoles with Unsaturated Compounds", March 22- December 31, 1967.

SYA = Sarvottam Y. Ambekar, postdoctoral research, 1968-69.

JBH = Joseph B. Hanson, NSF Undergraduate Research Participant, summers of 1965 and 1967.

DT = Dennis Toskas, NSF Undergraduate Academic Year Research Participant and senior thesis research, 1968.

References

- (a) M. M. Endicott, E. Wick, M. L. Mercury, and M. L. Sherrill, J. Amer. Chem. Soc., 68, 1299-1301 (1946).
- (b) Jack L. Pinkus, Univ. of Pittsburgh, Pittsburgh, Pa., personal communication (taken from a report to the National Institutes of Health), Oct. 5, 1966.
- (c) J. O. Bahls, Ph.D. thesis, Univ. of Minn., Aug. 1972, pp. 87-88; Diss. Abstr. Int. B., 33, 5723-5724 (1973).
- (d) D. A. Jones, Ph.D. thesis, Univ. of Minn., May 1961, pp. 81-82; Diss. Abstr., 22, 1828 (1961).
- (e) (a) F. Kröhnke and M. Meyer-Delius, Chem. Ber., 84, 932-941 (1951); (b) F. Kröhnke and I. Vogt, Chem. Ber., 85, 376-385 (1952).
- (f) R. F. Modler, Ph.D. thesis, Univ. of Minn., June 1965; Diss. Abstr., 26, 4244 (1966); (a) pp. 60-65; (b) pp. 102-105.
- (g) (a) W. E. Noland, K. R. Rush, and L. R. Smith, J. Org. Chem., 31, 65-69 (1966); (b) K. N. Campbell, J. Shavel, Jr., and B. K. Campbell, J. Amer. Chem. Soc., 75, 2400-2403 (1953).
- (h) (a) P. Pfeiffer, Chem. Ber., 45, 1819-1830 (1912); (b) P. Pfeiffer, S. Braude, R. Fritsch, W. Halberstadt, G. Kirchoff, J. Kléber, and P. Wittkop, Ann. Chem., 411, 72-158 (1916).
- (i) W. E. Noland and R. F. Modler, J. Amer. Chem. Soc., 86, 2086-2087 (1964).
- (j) (a) W. J. Adams, and D. H. Hey, J. Chem. Soc., 3254-3259 (1950); (b) R. C. Elderfield and J. B. Wright, J. Amer. Chem. Soc., 68, 1276-1277 (1946); (c) W. Wislicenus, K. Börner, P. Kurtz, and E. A. Bilhuber, Ann. Chem., 413, 206-252 (248-249) (1917).
- (k) Joseph B. Hanson (with W. E. Noland), National Science Foundation Undergraduate Research Participant, Univ. of Minn.; (a) Summer 1965; (b) Summer 1967.
- (l) (a) T. A. K. Smith and H. Stephen, Tetrahedron, 1, 38-44 (1957); (b) H. Stephen and G. Wadge, J. Chem. Soc., 4420-4421 (1956); (c) V. S. Patel and S. R. Patel, J. Indian Chem. Soc., 42, 531-535 (1965); (d) J. L. Rodgers and J. P. Milionis (to American Cyanamid Co.), U.S. Patent 3,169,129, Feb. 9, 1965; Chem. Abstr., 62, 14696a (1965) (the compounds are not listed in the abstract).
- (m) D. T. Zentmyer and E. C. Wagner, J. Org. Chem., 14, 967-981 (1949).
- (n) D. R. Desai, V. S. Patel, and S. R. Patel, J. Indian Chem. Soc., 43, 351-355 (1966).
- (o) Mark A. Jaglowski (with W. E. Noland), National Science Foundation Undergraduate Research Participant, University of Minn., Summer 1962.
- 41

References - continued

- (p) R. C. Elderfield and J. B. Wright, J. Amer. Chem. Soc., 68, 1276-1277 (1946).
- (q) Robert C. Krahn (with W. E. Noland), National Science Foundation Undergraduate Research Participant, University of Minn., Summer 1963.
- (r) J. B. Cohen and D. McCandlish, J. Chem. Soc., 87, 1271 (1905).

42

Personnel Receiving Contract Support

(including graduate degree received, if any)

In chronological order of employment:

- (1) Dr. Kung Tu Kuo, postdoctoral Research Specialist, June 23, 1967-Aug. 31, 1969, full time.
- (2) Robert J. Strange, Graduate Research Assistant, Aug. 16-Sept. 15, 1967, half time.
- (3) Dennis P. Landucci, Graduate Research Assistant, Sept. 1-15, 1967, half time. M.S. thesis Sept. 1969, on an unrelated subject: "A Study of the Bromination of Methylindoles and a Related Oxidation Product from 2,3-Dimethylindole".
- (4) Terrence R. Ashe, Undergraduate Research Assistant, Sept. 1, 1967-Oct. 31, 1968, part time.
- (5) Dr. M. Akram Sandhu, postdoctoral Research Specialist, Oct. 18, 1967-Nov. 15, 1969, full time.
- (6) Dr. Sarvottam Y. Ambekar, postdoctoral Research Specialist, Feb. 1, 1968-Aug. 31, 1969, full time.

Related Work Not Supported by the Contract

- (1) Joseph B. Hanson, NSF Undergraduate Research Participant, summer 1967, "Synthesis and Reactions of Ten Quinazolinones and Their Precursors".
- (2) Jerald K. Rasmussen, NSF Undergraduate Research Participant and senior thesis student, academic year 1967-68, "Synthesis and Ring Expansion of 2-(2-Pyridyl)isatogens".
- (3) Dennis Toskas, NSF Undergraduate Academic Year Research Participant and senior thesis student, winter and spring 1968, "Carbon and Nitrogen Ring Insertion Reactions of 2-Styrylisatogen".
- (4) Tetsuo Kakehi, M.S. thesis, Sept. 1969, "Ring Expansion Reactions of Biisatogens".
- (5) Lily C. Tomlin, M.S. thesis, April 1971, "Variation of Reagents in the Nitrogen Ring Expansion Reaction of 2-Phenylisatogen".
- (6) R. James Puhl, Ph.D. thesis, May 1971, "Reactions of Isatogen Analogs"; Diss. Abstr. Int. B, 32, 4498-4499 (1972).
- (7) Jerold O. Bahls, Ph.D. thesis, Aug. 1972, "Substituent Effects in Ring Expansion Reactions of Isatogens with Acetylenes"; Diss. Abstr. Int. B, 33, 5723-5724 (1973).